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**PROTOCOL**

**Peripheral and Macular Retinal Vascular Perfusion and Leakage Dynamics in Diabetic Macular Edema and Retinal Venous Occlusions During Intravitreal Aflibercept Injection (IAI) Treatment for Retinal Edema: PERMEATE Study**

**NCT NUMBER**

NCT02503540

**DOCUMENT DATE**

January 20, 2017

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## Clinical Study Protocol

*Peripheral and Macular Retinal Vascular Perfusion and Leakage Dynamics in Diabetic Macular Edema and Retinal Venous Occlusions During Intravitreal Aflibercept Injection (IAI) Treatment for Retinal Edema: PERMEATE Study*

**Compound:** Intravitreal aflibercept injection

**Study Name:** PERMEATE Study

**Clinical Phase:** Phase IV

**Date of Issue:** January 20, 2017

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**CLINICAL STUDY PROTOCOL SYNOPSIS**

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<b>TITLE</b>	<b>Peripheral and Macular Retinal Vascular Perfusion and Leakage Dynamics in Diabetic Macular Edema and Retinal Venous Occlusions During Intravitreal Aflibercept Injection (IAI) Treatment for Retinal Edema: PERMEATE Study</b>
<b>TITLE IN LAY TERMS</b>	Treatment of diabetic macular edema and retinal vein occlusions with IAI
<b>SITE LOCATION(S)</b>	
<b>Principal Investigator</b>	Justis P. Ehlers MD Cole Eye Institute Cleveland Clinic Cleveland, Ohio

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<b>OBJECTIVE(S)</b>	<p>This interventional study will evaluate the retinal vascular dynamics associated with IAI therapy in eyes with diabetic macular edema (DME) or macular edema secondary to retinal vein occlusion (RVO), as follows:</p> <p>(1) To characterize the longitudinal retinal vascular dynamics in DME and RVO in the retinal periphery and macular area over a 12-month period while being treated with IAI with a novel angiographic quantitative assessment tool.</p> <p>(2) To assess the efficacy and safety of IAI therapy based on assessment of the retinal vascular dynamics in DME and RVO.</p> <p>(3) To develop potential imaging biomarkers based on high-resolution quantitative analysis of ultra-widefield angiography and optical coherence tomography that are predictors of response to IAI therapy in DME and RVO.</p>
<b>STUDY DESIGN</b>	<p>This study is an interventional, single arm, investigator initiated study. Subjects will be given 2 mg (0.05 mL or 50 microliters) of IAI injection administered monthly for the first 6 months, followed by 2 mg (0.05 mL) once every 2 months. Each subject will be evaluated for 12 months. Thus, the study duration will be 12 months plus the recruitment period.</p> <p>Subjects will be evaluated every month for safety, efficacy as measured by SDOCT and best corrected visual acuity (BCVA) using the Electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) protocol. In addition, ultra-widefield angiography will be performed at baseline, month 3, month 6, month 9, and at the final visit.</p> <p>Only one eye per subject may be enrolled in the study. If a subject's fellow (non-study) eye requires treatment for at study entry, or during the subject's participation in the study, the fellow eye can receive IAI injection for DME or macular edema secondary to RVO.</p>
<b>STUDY DURATION</b>	12 Months

<b>ESTIMATED STUDY COMPLETION DATE</b>	February 1, 2018
<b>POPULATION</b>	
<b>Sample Size:</b>	30 Subjects
<b>Target Population:</b>	Patients presenting with foveal-involving macular edema secondary to diabetes and retinal vein occlusive disease
<b>TREATMENT(S)</b>	IAI injection will be supplied by Regeneron Pharmaceuticals, Inc. and will be administered using standard techniques.  Subjects will be given 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every month for the first 6 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 2 months.
<b>ENDPOINT(S)</b>	
<b>Primary:</b>	<ul style="list-style-type: none"> <li>▪ The primary study endpoint is the mean change in total leakage index at month 12 as measured by ultra-widefield angiography (defined as the proportion of retinal area involved in angiographic leakage).</li> </ul>
<b>Secondary:</b>	<p>Secondary endpoints would include</p> <ul style="list-style-type: none"> <li>▪ The mean change in total leakage index at month 6</li> <li>▪ The diabetic retinopathy severity at month 6 and 12 (if applicable)</li> <li>▪ The amount of hemorrhage at month 6 and 12</li> <li>▪ The change in ischemic index (defined as the proportion of retinal area with nonperfusion) at month 6 and 12</li> <li>▪ The mean absolute change from baseline central subfield thickness at month 6 and 12</li> <li>▪ The mean change from baseline in best-corrected visual acuity (BCVA) score at months 6 and 12</li> <li>▪ The percentage of subjects that were anatomically ‘dry’ by SDOCT at months 6 and 12,</li> <li>▪ The percentage of participants who gained or lost 10 letters or more of vision at months 6 and 12</li> <li>▪ The percentage of subjects who gained or lost 15 letters or more of vision at months 6 and 12</li> <li>▪ The percentage of patients that are 20/40 or better at months 6 and 12</li> </ul>

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- The percentage of patients that are 20/200 or worse at months 6 and 12
  - The incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs.

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**PROCEDURES AND ASSESSMENTS**

Ongoing assessments will include BCVA measurement, ophthalmic examinations and recording and evaluation of clinical adverse events. Subjects will undergo SDOCT at each visit. Ultra-widefield angiography will be performed at baseline, month 3, month 6, month 9 and month 12. Optional, OCT angiography will be performed at baseline, month 3, month 6, month 9, and month 12.

Subjects will be given 2 mg (0.05 mL or 50 microliters) IAI administered by intravitreal injection every month for the first 6 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 2 months. The fellow eye may also received IAI as needed for DME or macular edema secondary to RVO as determined by the investigator.

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**STATISTICAL PLAN**

The patients will be compared to their baseline measurement for the primary and secondary outcome. Trends and statistical significant difference will be reported.

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
CRF	Case report form
EC	Ethics Committee
eCRF	Electronic case report form
FAS	Full analysis set
ICF	Informed consent form
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event

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## 1. INTRODUCTION AND RATIONALE

### 1.1 Introduction

Diabetic macular edema (DME) is the most common cause of vision loss from diabetic retinopathy. It is characterized by macular swelling secondary to increased vascular permeability secondary to loss of pericytes in the macular vascular bed. Clinically, microaneurysms and exudates are often seen in association with macular edema. Foveal-involving cystic changes and macular edema can have significant impact on visual loss. Extent of perfusion and ischemia also is important for visual prognosis. Retinal vein occlusions (RVO) are the second most common retinal vascular disease following diabetic retinopathy. Vision loss from RVO most commonly results from macular edema and/or retinal ischemia.

VEGF is a homodimeric protein with a molecular weight of 34 to 42 kDa (Thickett, 1999). VEGF binds to and activates 2 high affinity receptors, Flt-1 (VEGFR1) and Flk-1 (VEGFR2), which are predominantly located on the vascular endothelium.

Multiple factors play a role in the evolution of diabetic macular edema and retinal venous occlusive disease. Vascular endothelial growth factor has been shown to be significantly elevated in diabetic retinopathy and may play an important role in the evolution and pathogenesis of DME. Increasing VEGF levels are also seen in the setting of progressive ischemia, such as proliferative diabetic retinopathy when extensive peripheral nonperfusion may be present (Wessel et al, 2012). Additionally significant peripheral vascular perfusion abnormalities are often seen in RVO (Singer et al, 2014). Reducing the active levels of VEGF may have significant positive consequences for outcomes related to DME and RVO management.

VEGF has 2 properties that explain its important roles in normal fetal development and in biology: VEGF is a powerful mitogen for endothelial cells (Ferrara et al., 1991), thus promoting formation of new vessels that are required for normal and pathological tissue growth (Ferrara, 2000; Ferrara and Davis-Smyth, 1997).

Injection of VEGF into the eye, or local over-expression of VEGF by transgenic methods, can induce vascular leakage and new blood vessel formation in the retina (Ohno-Matsui et al., 2002). Since VEGF appears to be a fundamental component of the process of vascular permeability, VEGF blockade constitutes a promising therapeutic approach in both DME and RVO.

IAI is a recombinantly produced fusion protein consisting of portions of the human VEGF receptor extracellular domains fused to the Fc domain of human IgG1 (Figure 1). IAI is comprised of portions of the extracellular domains of 2 different VEGF receptors. It contains sequences encoding Ig domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of the human IgG1 Fc domain. IAI is a dimeric glycoprotein with a protein molecular weight of 97 kDa, and contains ~15% glycosylation to give a total molecular weight of 115 kDa.

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**Figure 1. The IAI Molecule**

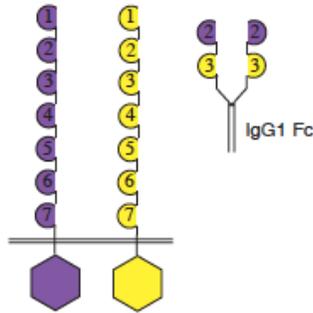


Figure 1. VEGFR1 and VEGFR2 are related receptors that have 7 Ig domains in the extracellular portion and a tyrosine kinase domain intracellularly. IAI contains the VEGFR1 Ig2 domain fused to the VEGFR2 Ig3 domain, which is in turn fused to the IgG1 Fc.

IAI has several potential advantages over other VEGF blockers: it has a much higher affinity ( $\sim 0.5$  pM dissociation constant for VEGF<sub>165</sub> and VEGF<sub>121</sub>) than a humanized monoclonal antibody. IAI also binds the related factors Placental Growth Factor 1 and 2 (PLGF1 and PLGF2), which may be advantageous in certain disease situations, including retinal neovascularization (Rakic et al 2003).

## 1.2 Rationale

### 1.2.1 Rationale for Study Design

Multiple phase III studies (e.g., COPERNICUS, GALILEO, VISTA, VIVID, VIBRANT), have evaluated intravitreal IAI for the management of DME and macular edema secondary to RVO. Results from these studies demonstrated clinical efficacy for IAI and significant improvements in visual acuity and macular thickness. In clinical practice, select patients continue to have variable response to anti-VEGF therapy including IAI. Preliminary studies have suggested that there is a significant amount of retinal vascular changes (e.g., increased permeability, ischemia) in the retinal periphery in both DME and RVO ((Singer et al, 2014; Wessel et al, 2012). Currently, assessment of angiographic phenotypes is limited primarily to subjective interpretation. However, new advances in technology now allow for objective quantitative assessment of angiographic parameters (see figures below). These global assessments of angiographic features, including leakage and ischemia, may allow for a better characterization of the disease burden and allow for the development of imaging biomarkers that have implications for therapeutic response or resistance. Additionally, preliminary reports have suggested that some features (such as ischemic load) may be dynamic and influenced by anti-VEGF therapy. This study will prospectively assess the alterations in angiographic parameters with a novel quantitative analysis tool to provide insights into the retinal vascular changes that occur during treatment with IAI and to examine the relationship between these features and treatment response.

Figure 1: Branch retinal vein occlusion with longitudinal angiography following anti-VEGF therapy with quantitative assessment of vascular leakage (green).

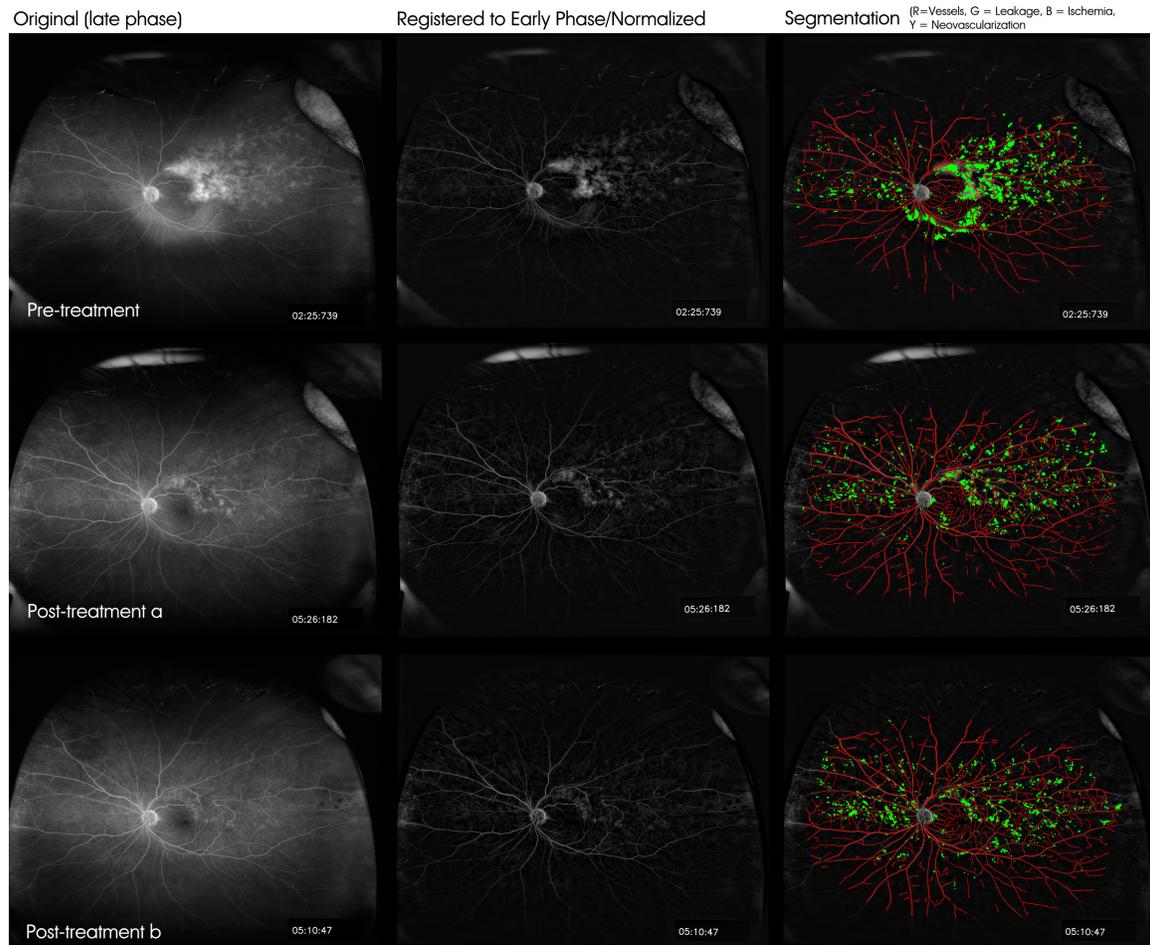
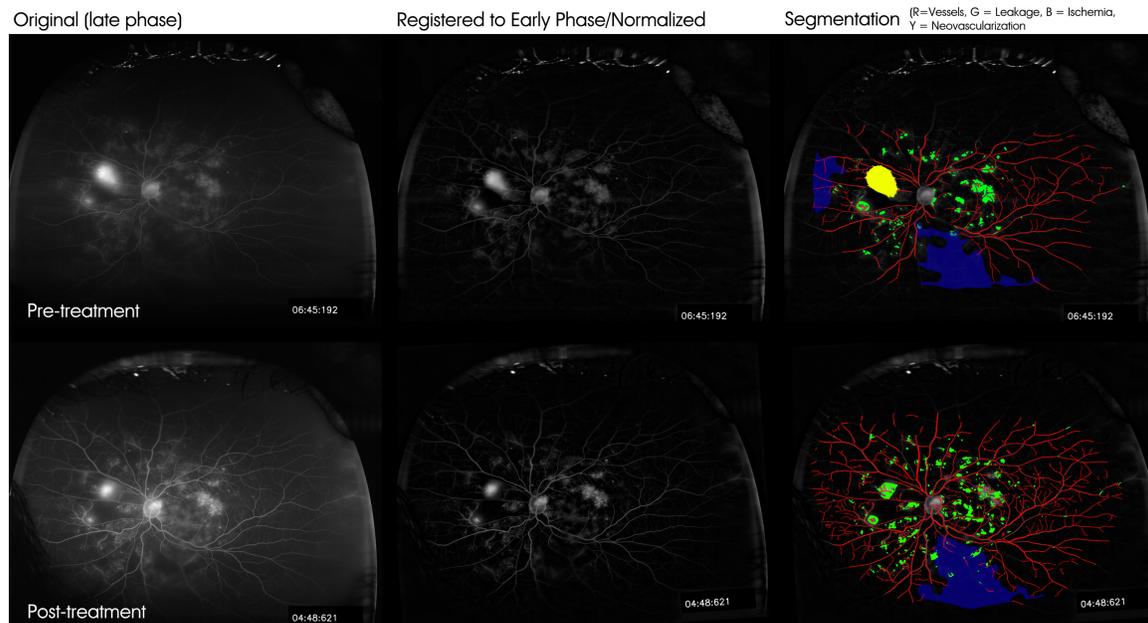


Figure 2: Diabetic macular edema and proliferative diabetic retinopathy with automated identification of neovascular leakage (yellow), ischemia (blue) and retinal vascular leakage (green). Longitudinal assessment following anti-VEGF treatment



## 1.2.2 Rationale for Dose Selection

The dose and treatment regimen was selected based on the phase III studies and the drug package insert. Specifically, subjects will be given 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every month for the first 6 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 2 months.

## 2. STUDY OBJECTIVES

### 2.1 Primary Objective

To characterize the longitudinal retinal vascular dynamics in DME and RVO in the retinal periphery and macular area over a 12-month period while being treated with IAI with a novel angiographic quantitative assessment tool.

### 2.2 Secondary Objective(s)

- (1) To assess the efficacy and safety of IAI therapy for DME and RVO-related DME in treatment naïve eyes.
- (2) To develop potential imaging biomarkers based on high-resolution quantitative analysis of ultra-widefield angiography and optical coherence tomography that are predictors of response to IAI therapy in DME and RVO.

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## **STUDY DESIGN**

### **2.3 Study Description and Duration**

Subjects will be assigned to treatment with 2 mg IAI (0.05 mL or 50 microliters) administered monthly for the first 6 months, followed by 2 mg (0.05 mL) once every 2 months. Criteria for additional monthly treatment has been defined for subjects following the initial 6 months of the study.

The planned enrollment for the 30 subjects needed for this study is estimated to be 12 months. The study duration for each subject is scheduled to be 12 months. Evaluations will occur every month for the duration of the study. OCT examinations will be conducted at every visit.

Only one eye will be designated as the study eye. For subjects who meet eligibility criteria in both eyes, the investigator and patient will select the study eye.

### **2.4 Study Committees**

Appropriate action, if needed, will be taken based upon this review and in consultation with the principal investigator. All events will be managed and reported in compliance with all applicable regulations and included in the final clinical study report.

## **3. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS**

### **3.1 Number of Subjects Planned**

The target enrollment for this study is 30 subjects.

### **3.2 Study Population**

Subjects will be recruited through clinics at the Cole Eye Institute, Cleveland OH and Cole Eye satellite offices. The study will seek approval from the Cleveland Clinic Investigational Review Board (IRB) and all study related procedures will be performed in accordance with the Declaration of Helsinki and US Code 21 of Federal Regulations.

All study-related procedures will be performed at Cole Eye Institute, Cleveland Clinic Main Campus or Cole Eye Hillcrest.

#### **3.2.1**

#### **Inclusion Criteria**

A subject must meet the following criteria to be eligible for inclusion in the study:

1. Signed Informed Consent.
2. Men and women  $\geq 18$  years of age.
3. Foveal-involving retinal edema secondary to DME or RVO based on investigator review of SDOCT.

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4. E-ETDRS best-corrected visual acuity of: 20/25 to hand motions in the study eye.
  5. Willing, committed, and able to return for ALL clinic visits and complete all study related procedures.
  6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

### **Exclusion Criteria**

A subject who meets any of the following criteria will be excluded from the study:

1. Any prior or concomitant therapy with another investigational agent to treat DME or RVO in the study eye.
2. Prior panretinal photocoagulation in the study eye.
3. Prior intravitreal anti-VEGF therapy in the study eye.
4. Prior focal/grid laser photocoagulation in the study eye.
5. Prior history of intravitreal steroid therapy in the study eye.
6. Any history of allergy to fluorescein sodium or other reason that the patient is unable to undergo fluorescein angiography (e.g., inability to get vascular access, unable to tolerate procedure)
7. Prior systemic anti-VEGF therapy, investigational or FDA-approved, is only allowed up to 3 months prior to first dose, and will not be allowed during the study.
8. Significant vitreous hemorrhage obscuring view to the macula or the retinal periphery as determined by the investigator on clinical exam and ultra-widefield angiography.
9. Presence of other causes of macular edema, including myopic degeneration, ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, choroidal neovascularization, neovascular age-related macular degeneration or multifocal choroiditis in the study eye. Epiretinal membranes are allowed.
10. Presence of macula-threatening traction retinal detachment.
11. Prior vitrectomy in the study eye.
12. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
13. Any history of macular hole of stage 2 and above in the study eye.
14. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as it's unlikely to interfere with the injection.
15. Prior trabeculectomy or other filtration surgery in the study eye.

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16. Uncontrolled glaucoma at baseline evaluation (defined as intraocular pressure  $\geq 25$  mmHg despite treatment with anti-glaucoma medication) in the study eye.
  17. Active intraocular inflammation in either eye.
  18. Active ocular or periocular infection in either eye.
  19. Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye.
  20. Any history of uveitis in either eye.
  21. Active scleritis or episcleritis in either eye.
  22. Presence or history of scleromalacia in either eye.
  23. Aphakia in the study eye.
  24. Previous therapeutic radiation in the region of the study eye.
  25. History of full-thickness penetrating keratoplasty in the study eye. Partial thickness corneal transplants, including DSAEK and DMEK are allowed.
  26. Significant media opacities, including cataract, in the study eye which might interfere with visual acuity, assessment of safety, or fundus photography.
  27. Any concurrent intraocular condition in the study eye (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the 52 week study period.
  28. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the subject beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety.
  29. Participation as a subject in any clinical study within the 12 weeks prior to Day 1.
  30. Any systemic therapy with an investigational agent in the past 3 months prior to Day 1.
  31. Any history of allergy to povidone iodine.
  32. Pregnant or breast-feeding women
  33. Women of childbearing potential\* who are unwilling to practice adequate contraception during the study (adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly)

\*Postmenopausal women must be amenorrheic for at least 12 months in order **not** to be considered of child bearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

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### **3.3 Premature Withdrawal from the Study**

A subject has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator has the right to withdraw a subject from the study in the event of an intercurrent illness, AE, treatment failure, protocol violation, cure, and for administrative or other reasons. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subject should be avoided.

Should a subject (or a subject's legally authorized guardian or representative) decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. Early termination procedures should be followed, as delineated in [section 5.2.4](#).

### **3.4 Replacement of Subjects**

Subjects prematurely discontinued from the study prior to visit 4 may be replaced at PI discretion.

## **4. STUDY TREATMENTS**

Subjects will be assigned to treatment with 2 mg intravitreal IAI injection (0.05 mL or 50 microliters) administered monthly for the first 6 months, followed by 2 mg (0.05 mL) once every 2 months.

### **4.1 Additional Treatment**

Additional treatment with IAI can be applied, if the subject experiences any of the following events within 56 days since the last treatment:

- Loss of 10 or more ETDRS letters from best previous measurement
- Increase in 75 microns of retinal thickness as compared to the best previous visit.

If the subject meets additional treatment criteria at any time during the study, the subject can receive additional IAI at least every 28 days. Additional treatment can be withheld by the treating investigator if in the opinion of the investigator, additional treatment will not provide benefit.

### **4.2 Dose Modification and Stopping Rules**

#### **4.2.1 Dose Modification**

Dose modification for an individual subject is not allowed.

#### **4.2.2 Study Drug Stopping Rules**

Information on follow-up for subjects who permanently discontinue from study drug, but choose to remain in the study is provided in [section 6.2.4](#).

### **4.3 Method of Treatment Assignment**

All subjects are enrolled in the same cohort to receive treatment with intravitreal aflibercept injection.

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#### **4.3.1 Blinding/Masking**

This is a single arm treatment study and the patients and physicians will be aware of their current treatment assignment and schema.

#### **4.3.2 Packaging, Labeling, and Storage**

2.0 mg intravitreal IAI injection is formulated as a sterile liquid to a final concentration of 40 mg/mL intravitreal IAI injection in 5% sucrose, 10 mM sodium phosphate pH 6.3, 0.03% polysorbate 20, and 40 mM NaCl. Intravitreal IAI injection 2.0 mg study drug will be supplied by Regeneron Pharmaceuticals Inc. in sealed, sterile 3 mL vials with a “withdrawable” volume of approximately 0.5 mL. Vials must be used only once (defined as entered with a needle). The volume of injection will be 0.05 mL for the 2 mg dose. For study drug in vials, the study drug will be withdrawn using aseptic technique.

Study drug will be shipped to the site via overnight shipping using cold packs to maintain a temperature of 2° to 8° C. The Investigator, or an approved representative (e.g. pharmacist), will ensure that all study drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. The shipping box is to be opened and stored immediately at the site in a refrigerator intended for investigational products at a temperature of 2° to 8°C.

When vials are removed from the refrigerator, the solution should be visually inspected and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Exposure of the material to temperatures outside these limits, except for warming prior to administration, is not recommended and may result in loss of activity. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained; and must include a record of the dates, when the refrigerator was checked, the initials of person checking, and the temperature.

#### **4.3.3 Supply and Disposition of Treatments**

Study drug will be shipped at a temperature of 2° to 8°C to the investigator or designee at regular intervals or as needed during the study. At the end of the study, and following drug reconciliation and documentation, all opened and unopened vials of study drug will be destroyed or returned to Regeneron Pharmaceuticals, Inc. or designee.

#### **4.3.4 Treatment Accountability**

All drug accountability records will be kept current.

The investigator will account for all opened and unopened vials of study drug. These records will contain the dates, quantity, and study medication

- dispensed to each patient – or -
- disposed of at the site or returned to Regeneron Pharmaceuticals, Inc. or designee.

All accountability records will be made available for inspection by regulatory agency inspectors.

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#### **4.3.5 Treatment Compliance**

All drug compliance records must be kept current and must be made available for inspection by regulatory agency inspectors.

#### **4.4 Concomitant Medications and Procedures**

Subjects may not receive any medications (approved or investigational) for their DME and RVO in the study eye other than the assigned study treatment (IAI as specified in this protocol, until they have completed the end of study (12 months) or ET visit assessments. This includes medications administered locally (eg, IVT, topical, juxtasclear or periorbital routes), as well as those administered systemically, with the intent of treating the study and/or fellow eye. Laser photocoagulation procedures will not be allowed during the first six months of the study. After six months, focal/grid laser photocoagulation can be performed at the discretion of the investigator for persistent macular edema. After six months, panretinal laser photocoagulation can be performed for the presence of proliferative disease with vitreous hemorrhage or other high risk characteristics (e.g., neovascularization of the disc). If neovascularization was present at baseline, panretinal photocoagulation is encouraged at study exit to avoid rebound neovascularization if not performed during the study for high-risk characteristics.

If a subject's fellow (non-study) eye requires treatment for DME or RVO at study entry, or during the subject's participation in the study, the fellow eye can receive IAI. Intravitreal aflibercept injection will be provided at no cost by Regeneron for the fellow eye. Although the fellow eye can receive treatment, it will not be considered an additional study eye. The fellow eye may also receive laser photocoagulation, as needed, at investigator discretion.

#### **4.4.1 Permitted Medications and Procedures**

Any other medication that are considered necessary for the subject's welfare, and that are not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

#### **4.4.2 Prohibited Medications and Procedures**

Systemic anti-angiogenic agents will not be permitted during the study.

#### **4.5 Post-Study Treatment**

All medications are permitted post-study treatment.

### **5. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS**

#### **5.1 Schedule of Events**

Study assessments and procedures are presented by study period and visit in [Table 1](#).

**Table 1 Schedule of Events**

Study Procedure	Treatment Period (Visit intervals after baseline are 28 days since last visit +/- 7 days)												Additional	
	Screening & Baseline Visit 1	2	3	4	5	6	7*	8	9*	10	11*	12	End of Treatment Visit 13	Unscheduled Follow up Visit
Day/Month	Month 0	M 1 28 days +/- 7 days	M 2 28 days +/- 7 days	M 3 28 days +/- 7 days	M 4 28 days +/- 7 days	M 5 28 days +/- 7 days	M 6 28 days +/- 7 days	M 7 28 days +/- 7 days	M 8 28 days +/- 7 days	M 9 28 days +/- 7 days	M 10 28 days +/- 7 days	M 11 28 days +/- 7 days	Month 12 +/-7 days	NA
Inclusion/Exclusion	x													
Informed Consent	x													
Medical History	x													
Demographics	x													
ETDRS Manifest Refraction/Slit Lamp/Tonometry/Fundus Exam study eye	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ultra-widefield Fluorescein angiogram	x			x			x			x			x	***
SDOCT study eye	x	x	x	x	x	x	x	x	x	x	x	x	x	X***
SDOCT angiography **	x			x			x			x			x	***
Administer Study Drug (intravitreal IAI injection)	x	x	x	x	x	x		x		x		x	x	***
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x

\* Additional treatment with intravitreal IAI injection if criteria met;

\*\* OCT angiography is optional at month 0, 3, 6, 9 and 12, and will not be performed at other timepoints.; \*\*\* at investigator’s discretion

## **5.2 Study Visit Descriptions**

### **5.2.1 Screening/Baseline Visit, Day 0,**

After the subject has provided informed consent, the following information will be collected:

- Inclusion/exclusion
- Informed consent documentation
- Demographics
- Medical history and concurrent illnesses
- Concomitant medications

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Tonometry
- Spectral Domain OCT evaluation
- Spectral Domain OCT angiography (optional)
- Ultra-widefield fluorescein angiogram
- Intravitreal aflibercept injection

### **5.2.2 Follow-up Period**

#### **5.2.2.1 *Month 1--Month 5 (+/- 7 Days)***

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Tonometry
- Spectral Domain OCT evaluation
- Spectral Domain OCT angiography (month 3 only; optional)

- Ultra-widefield fluorescein angiography (month 3 only)
- Intravitreal aflibercept injection

#### **5.2.2.2     *Months 6, 8, and 10 (+/- 7 Days)***

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Tonometry
- Spectral Domain OCT evaluation
- Spectral Domain OCT angiography (month 6 only; optional)
- Ultra-widefield fluorescein angiography (month 6 only)
- Intravitreal aflibercept injection (if additional treatment criteria is met)

#### **5.2.2.3     *Months 7, 9, and 11 (+/- 7 Days)***

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Tonometry
- Spectral Domain OCT evaluation
- Spectral Domain OCT angiography (month 9 only; optional)
- Ultra-widefield fluorescein angiography (month 9 only)
- Intravitreal aflibercept injection

#### **5.2.2.4 End of Treatment/Month 12 (+/- 7 Days)/Early Termination visit**

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination
- Fundus examination
- Tonometry
- Spectral Domain OCT evaluation
- Spectral Domain OCT angiography (month 12 only; optional)
- Ultra-widefield fluorescein angiography

#### **5.2.3 Additional Visits**

##### **5.2.3.1 *Unscheduled visit***

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments may be conducted:

- ETDRS visual acuity with manifest refraction in both eyes
- Slit lamp examination at investigator's discretion
- Fundus examination at investigator's discretion
- Spectral Domain OCT evaluation at investigator's discretion
- Intravitreal injection of aflibercept (if criteria for additional treatment met) in study eye
- Intravitreal injection of aflibercept in fellow eye (if needed)

#### **5.2.4 Early Termination Visit**

Subjects who are withdrawn from the study should be instructed to return to the clinic for end of study assessments.

### **5.2.5      **Unscheduled Visits****

All attempts should be made to keep subjects on the study schedule.  Unscheduled visits may be necessary to repeat testing following AEs, or for any other reason, as warranted.

## **5.3           **Study Procedures****

### **5.3.1       **Procedures Performed only at the Screening/Baseline Visit****

No specific procedures other than above will be performed for the sole purpose of determining study eligibility or characterizing the baseline population.

### **5.3.2       **Efficacy Procedures****

**Vision:** Visual Acuity Visual function of the study eye and the fellow eye will be assessed using the E-ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985). Visual Acuity examiners must be certified to ensure consistent measurement of BCVA.

**Spectral Domain Optical Coherence Tomography (OCT):** Retinal characteristics will be evaluated using SDOCT on the study eye. At the Screen Visit (Visit 1) images will be captured and archived. The scanning protocol will consist of fast macular thickness maps as well as high definition 6.0 mm linear scans centered on the fovea. OCT scans will be recorded by scoring their morphological patterns, and by recording the foveal minimum and volumetric analysis for each subject (Cirrus OCT, Zeiss, San Leandro, CA, software version 5.0). OCT images will read by a trained reader and also assessed with a computerized segmentation analysis tool.

### **Fundus Evaluation, Fundus Photography, and Fluorescein Angiography (FA):**

The anatomical state of the retinal vasculature of the study eye will be evaluated by funduscopic examination. Ultra-widefield fluorescein angiography will be performed at the baseline visit, month 3, month 6, month 9, and at the month 12 visit. Angiographic analysis will be performed by a trained reader and a computerized analysis tool. Optional spectral domain OCT angiography will be performed at month 3, month 6, month 9, and at month 12 (Avanti XR, Optovue, CA). At no other time points will OCT angiography be performed. OCT angiography is non-invasive, non-contact diagnostic test that utilizes special software to convert the traditional OCT information into vascular network map. No injection of dye is required for OCT angiography.

### **Intraocular Pressure:**

Intraocular pressure (IOP) of the study eye will be measured using applanation tonometry or Tonopen. The same method of IOP measurement must be used in each subject throughout the study.

### 5.3.3 Safety Procedures

#### 5.3.3.1 Adverse Event Information Collection

The investigator (or designee) will record all AEs that occur during the study following the baseline visit. Information on follow-up for AEs is provided in [section 6.2.4](#).

The definition of an AE and SAE, and information on the determination of severity and relationship to treatment are provided in [section 6](#).

## 6. SAFETY DEFINITIONS, REPORTING, AND MONITORING

### 6.1 Definitions

#### 6.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (i.e. any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

#### 6.1.2 Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (e.g. a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or prolongation of existing hospitalization. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse). Any

malignancy (other than basal cell skin cancers) would be considered a medically important event.

## **6.2 Recording and Reporting Adverse Events**

All AEs and SAEs will be recorded in the patient's source documents. Laboratory values or vital signs will be recorded as AEs only if they are medically relevant.

All SAEs, regardless of assessment of causal relationship to study drug will be reported to Regeneron Pharmaceuticals, Inc.

The investigator will promptly report to the IRB all unanticipated problems involving risks to subjects. This includes death from any cause and all SAEs related to the use of the study drug. All SAEs will be reported to the IRB, regardless of assessed causality.

### **6.2.1 Deaths**

Any AE that results in death is considered a SAE. Deaths that occur from the time the patient signs the informed consent form ("ICF") until 30 days after dosing will be reported to the appropriate IRB and to Regeneron Pharmacovigilance and Risk Management (or designee) within 24 hours of learning of the death.

Any available autopsy reports and relevant medical reports will be sent to Regeneron Pharmaceuticals, Inc. as soon as possible.

To report an SAE, Regeneron will be contacted at the following:

[Medical.safety@regeneron.com](mailto:Medical.safety@regeneron.com)

**Fax 914-345-7476**

**SAE hotline: 914-593-1504**

### **6.2.2 Pregnancy and Other Events that Require Accelerated Reporting**

The following events will be reported to Regeneron Pharmaceuticals, Inc. within 24 hours of learning of the event:

**Overdose:** Accidental or intentional overdose of the study drug or concomitant medication, whether or not it is considered an AE.

**Pregnancy:** Although it is not considered an AE, the investigator will report to Regeneron Pharmaceuticals, Inc., any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 30 days following the last dose of study drug. The investigator will follow the pregnancy until delivery, or longer. If the pregnancy continues to term (delivery), the health of the infant will also be reported to Regeneron Pharmaceuticals, Inc.

To report an SAE, Regeneron will be contacted at the following:

[Medical.safety@regeneron.com](mailto:Medical.safety@regeneron.com)

**Fax 914-345-7476**

**SAE hotline: 914-593-1504**

### 6.2.3 Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study will be reported to Regeneron Pharmaceuticals Inc. within 30 days. All SAEs leading to a patient's withdrawal from the study will be reported. To report an SAE, Regeneron will be contacted at the following:

[Medical.safety@regeneron.com](mailto:Medical.safety@regeneron.com)

Fax 914-345-7476

SAE hotline: 914-593-1504

### 6.2.4 Follow-up

Adverse event information will be collected until the end of study visit, or the early termination visit, if the patient withdraws consent.

The investigator must make every effort to obtain follow-up information on the outcome of any SAE until the event is considered chronic and/or stable.

## 6.3 Evaluation of Severity and Causality

### 6.3.1 Evaluation of Severity

The severity of an AE will be graded by the investigator using a 3–point scale (mild, moderate, or severe) and reported in detail as indicated on the CRF and/or SAE form, as appropriate.

- **Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

### 6.3.2 Evaluation of Causality

The relationship to treatment will be determined by the investigator and reported on the CRF and/or SAE form, as appropriate. The following terms will be used:

**Not Related:** likely or clearly due to causes other than the study drug.

**Related:** possibly, probably, or definitely related to the study drug.

## **7. STUDY VARIABLES**

### **7.1 Demographic and Baseline Characteristics**

Baseline characteristics will include standard demography (eg, age, race, etc.), disease characteristics including medical history, and medication history for each subject.

### **7.2 Primary and Secondary Endpoints**

#### **Primary Endpoint:**

- The primary study endpoint is the mean change in total leakage index at month 12 as measured by ultra-widefield angiography (defined as the proportion of retinal area involved in angiographic leakage).

#### **Secondary Endpoint:**

- The mean change in total leakage index at month 6
- The diabetic retinopathy severity at month 6 and 12 (if applicable)
- The amount hemorrhage at month 6 and 12
- The change in ischemic index (defined as the proportion of retinal area with nonperfusion) at month 6 and 12
- The mean absolute change from baseline central subfield thickness at month 6 and 12
- The mean change from baseline in best-corrected visual acuity (BCVA) score at months 6 and 12
- The percentage of subjects that were anatomically ‘dry’ by SDOCT at months 6 and 12,
- The percentage of participants who gained or lost 10 letters or more of vision at months 6 and 12
- The percentage of subjects who gained or lost 15 letters or more of vision at months 6 and 12
- The percentage of patients that are 20/40 or better at months 6 and 12
- The percentage of patients that are 20/200 or worse at months 6 and 12
- The incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs.

### **7.3 Analysis Sets**

#### **7.3.1 Efficacy Analysis Sets**

The full analysis set (FAS) includes all subjects who received any study drug. Efficacy endpoints will be analyzed using the FAS.

#### **7.3.2 Safety Analysis Set**

The safety analysis set (SAF) includes all subjects who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

## **7.4 Subject Disposition**

The following will be provided:

- The total number of enrolled subjects
- The total number of subjects who discontinued the study, and the reasons for discontinuation
- A listing of subjects prematurely discontinued from treatment, along with reasons for discontinuation

## **7.5 Statistical Methods**

### **7.5.1 Demography and Baseline Characteristics**

Demographic and baseline characteristics will be summarized descriptively by treatment group. Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

### **7.5.2 Efficacy Analyses**

#### **7.5.2.1 Primary Efficacy Analysis**

The primary efficacy variable will be the mean change in total leakage index at month 12 as measured by ultra-widefield angiography (defined as the proportion of retinal area involved in angiographic leakage).

#### **7.5.2.2 Secondary Efficacy Analysis**

Secondary efficacy variables include the following:

- The mean change in total leakage index at month 6
- Diabetic retinopathy severity at month 6 and 12 (if applicable)
- Amount of retinal hemorrhage at month 6 and 12 for RVO (if applicable)
- Change in ischemic index (defined as the proportion of retinal area with nonperfusion) at month 6 and 12
- Mean absolute change from baseline central subfield thickness at month 6 and 12
- Mean change from baseline in best-corrected visual acuity (BCVA) score at months 6 and 12
- Percentage of subjects that were anatomically ‘dry’ by SDOCT at months 6 and 12
- Percentage of participants who gained 10 letters or more of vision at months 6 and 12
- Percentage of participants who lost 10 letters or more of vision at months 6 and 12
- Percentage of participants who gained 15 letters or more of vision at months 6 and 12

- Percentage of subjects who lost 15 letters or more of vision at months 6 and 12
- Percentage of patients that are 20/40 or better at months 6 and 12
- Percentage of patients that are 20/200 or worse at months 6 and 12

### **7.5.3 Safety Analysis**

#### **7.5.3.1 Adverse Events**

##### **Definitions**

For safety variables, two observation periods are defined:

- The treatment period is defined as the day from first dose of study drug to the last dose of study drug.
- The post-treatment period is defined as the time after the last dose of study drug.

Treatment-emergent AEs (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

##### **Analysis**

- Incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs

## **8. DATA MANAGEMENT AND ELECTRONIC SYSTEMS**

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at the Cleveland Clinic.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, applicable baseline findings, medication, medical history / surgical history/ophthalmic history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with a paper Data Capture tool.

### **8.1 Electronic Systems**

Electronic systems used to process and/or collect data in this study will include the following:

- Epic– EMR system
- Statistical Analysis Software (SAS) – statistical review and analysis

## **9. STUDY MONITORING**

### **9.1 Monitoring of Study Sites**

The study coordinator will review all documentation prior to enrollment of the first subject, and periodically during the study. In accordance with International Conference on Harmonization (ICH) guidelines, the coordinator will compare the eCRF entries with the appropriate source documents. Additional review may include, but is not limited to, subject ICFs, documentation of subject recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the designee upon request.

### **9.2 Source Document Requirements**

Investigators are required to prepare and maintain adequate and accurate subject records (source documents).

The investigator must keep all source documents on file with the CRF. Case report forms and source documents must be available at all times for inspection by authorized representatives of the designee and regulatory authorities.

### **9.3 Case Report Form Requirements**

A CRF for each subject enrolled in the study must be completed and signed by the study investigator or authorized designee. The CRF must be typed or filled out using indelible ink. The writing must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or authorized designee. The investigator must ensure the accuracy, completeness, legibility, and timeliness of the data reported to the designee in the CRFs. Case report forms must be available at all times for inspection by authorized representatives of the designee and regulatory authorities.

## **10. AUDITS AND INSPECTIONS**

This study may be subject to a quality assurance audit or inspection by authorities. Should this occur, the investigator is responsible for:

- Informing the designee of a planned inspection by the authorities as soon as notification is received, and authorizing the designee's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the designee immediately
- Taking all appropriate measures requested by the designee to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the designee may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

## **11. ETHICAL AND REGULATORY CONSIDERATIONS**

### **11.1 Good Clinical Practice Statement**

It is the responsibility of both the designee and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

### **11.2 Informed Consent**

The principles of informed consent are described in ICH Guidelines for GCP.

Regeneron will have the right to review and comment on the informed consent form.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each subject prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the subject in language that he/she can understand. The ICF should be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

- Subjects who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Subjects who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the subject's study record, and a copy of the signed ICF must be given to the subject.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study subjects must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the subject's study record and a copy must be given to the subject.

### **11.3 Subject Confidentiality and Data Protection**

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. Subjects should be identified by their initials and a subject identification number, only, on CRFs or other documents submitted to the designee. Documents that will not be submitted to the designee (eg, signed ICF) must be kept in strict confidence.

The subject's and investigator's personal data, which may be included in the investigator's study database, will be treated in compliance with all applicable laws and regulations. The investigator shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

### **11.4 Institutional Review Board**

An appropriately constituted IRB, as described in ICH Guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the subjects (eg, advertising) before any subject may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the IRB should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB should be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study.

A copy of the IRB approval letter with a current list of the IRB members and their functions must be received by Regeneron prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

## **12. PROTOCOL AMENDMENTS**

The investigator may not implement a change in the design or operation of the protocol or ICF without an IRB approved amendment.

## **13. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE**

### **13.1 Premature Termination of the Study**

Cleveland Clinic or Regeneron has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others.

## **14. STUDY DOCUMENTATION**

### **14.1 Certification of Accuracy of Data**

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the designee with the final set of CRFs for each subject.

### **14.2 Retention of Records**

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 2 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the designee before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the designee and the relevant records will be transferred to a mutually agreed-upon destination.

## 15. Appendix 1: Injection Procedure

Intravitreal aflibercept injection is formulated as a sterile liquid to a final concentration of 40 mg/mL. The volume of injection will be 50 µl (0.05 mL) for the 2 mg dose of IAI.

- Preparation (please see below regarding the optional use of topical antibiotic agents pre and post dose):
  - a. Apply topical anesthetic with or without subconjunctival anesthetic
  - b. Apply povidone iodine to eyelid margins, eyelashes, and conjunctival surface. For patients who have a known sensitivity to povidone iodine, another equally effective agent may be used.
  - c. Place 1 or 2 drops of povidone-iodine on the ocular surface at the intended injection site.
  - d. A sterile speculum may be used.
  - e. Mark the injection site location with a empty Tb syringe.
  - f. Apply additional drop of povidone-iodine to site of injection.
  
- Study Drug (VEGF Trap-Eye) Administration:
  - a. Insert needle at marked injection point.
  - b. Gently inject study drug.
  - c. As the needle is withdrawn, a sterile cotton tip applicator may be rolled over the entry site to minimize the risk of drug reflux.
  
- Post-Injection Procedures

Confirm that the patient has at least counting fingers vision. See guidelines below for additional post-injection management procedures.

### ***Guidelines for Pre and Post-injection Management***

- Use of Topical Antibiotic Agents

No pre or post-injection antibiotics will be used.

- If vision is less than Counting Fingers:

Visualize the optic nerve to verify reperfusion of the central retinal artery in the immediate post-injection period.

Check the IOP while maintaining a clean field. Monitor the IOP closely until it is below 30 mm Hg. If a Tono-pen™ is used to check pressure, a clean Tono-pen™ condom should be placed on the tip before taking each measurement. If Goldmann applanation tonometry is used, the applanator tip should be swabbed with alcohol and let to dry before using it to measure IOP. IOP may be lowered by pharmaceutical or surgical intervention, if required. Treatment should be initiated whenever IOP is increased to the extent that the central retinal artery remains closed or the patient remains less than count fingers for more than 1 to 2 minutes with an IOP > 35 mm Hg.

- Discharge

No special precautions are required before discharge of a patient who has had an uneventful recovery from intravitreal injection, but patients and/or caregivers should be educated to avoid rubbing the eye and to recognize the signs and symptoms of endophthalmitis, retinal detachment, or intraocular hemorrhage; these are eye pain or increased discomfort, increased redness of the eye (compared to immediately after injection), blurred or decreased vision, and increased ocular sensitivity to light.

## 16. Appendix 2: References

1. Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. *Endocr Rev.* 1997 Feb;18(1):4-25.
2. Ferrara N, Houck KA, Jakeman LB, Winer J, Leung DW. The vascular endothelial growth factor family of polypeptides. *J Cell Biochem.* 1991 Nov;47(3):211-8.
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